LONG-TERM FOLLOW-UP OF MEDICALLY TREATED PATIENTS WITH CORONARY ARTERY DISEASE

—I Incidence of Major Cardiac Events and Its Risk Factors in Japanese with Coronary Artery Disease—

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In the cooperative, multi-center trial, 491 medically treated patients with coronary artery disease were thoroughly assessed and followed for an average of 49 months. The rate of cardiac death and/or non-fatal myocardial infarction was 9.8%; 64% of cardiac events were fatal. Three factors, such as number of diseased coronary arteries, other diseased organs and the cardiothoracic ratio, contributed significantly to the evolution of cardiac events. The outcome of cardiac events in Japan in the period from 1973 to 1985 in patients with coronary artery disease was more favorable than those reported recently in the United States. The results of this study will serve as a control data base for further studies in Japan.

THE study of the natural course of ischemic heart disease is important because the information obtained can serve as a basis for the evaluation of various treatment approaches as well as provide valuable data for the assessment of such influences as race and culture. However, in this era of aggressive surgical treatment, with the wide use of coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), the patient populations available for such a study are not fully representative. That is these populations might be

comprised primarily of patients whose disease is too mild to warrant surgery or those who are too ill to withstand surgery. Therefore, any investigation of the natural history of ischemic heart disease should meet at least two requirements: 1) It should be planned so that the number of surgical candidates is relatively small, in other words, the patient population should be as homogeneous as possible, and 2) It should include assessment of at least one consistent predictive factor, such as the extent of coronary artery pathology, that would be comparable with predictive factors employed in future studies.

In contrast to numerous reports from Western

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Fig.1. Location of the nine participating institutions in Japan.

countries,¹⁻³ in Japan there have been few follow-up studies involving the precise assessment of coronary artery disease and including a reasonable number of patient. Although it has been reported that both the incidence and mortality of ischemic heart disease are lower in Japan than in Western countries,⁴⁻⁸ no coronary artery disease matched studies in Japan are available. In addition, it has become difficult to evaluate the natural course of patients with ischemic heart disease, due to the increasing use of PTCA and/or revascularization and CABG. The purpose of this large, multi-center study was to determine the incidence of major cardiac events in primarily non-surgical patients with thoroughly docu-

TABLE 1 DEFINITION OF CARDIAC EVENTS

Myocardial infarction: Chest oppression persisting more than 30 min, new appearance of Q waves, decrease in R wave voltage or changes in S-T segment and T waves on ECG; more than three-fold elevation of serum creatine kinase (MB isozyme) over normal upper limits.

Transmural myocardial infarction: Abnormal Q waves or decrease in amplitude of R waves on ECG and/or localized abnormal wall motion of left ventriculogram.

Subendocardial myocardial infarction: S-T segment depression and T wave changes without new Q or R wave abnormality; greater than three-fold elevation of creatine kinase (MB) is essential.

Anterior myocardial infarction: Above-mentioned ECG abnormalities localized at V_2-V_6 , I, and aV_L , and/or abnormal wall motion at segments 1, 2, 3, and 6 (American Heart Association definition).

Inferior myocardial infarction: Abnormal findings at II, III, or aV_F on ECG and/or segments 4, 5, and 7 on left ventriculogram.

Angina Pectoris: Transient ischemic events with typical chest oppression, resolving within 5 min (within 30 min when the attack occurs at rest) with rest or sublingual administration of nitrates, and documented S-T, T changes during more than one attack or with provocation test. Attacks which occurred within 1 month of recent MI were excluded.

Unstable angina: The 2 month-period following the appearances of any of the three conditions described below was designated as unstable angina.

- 1) **Angina of new onset:** Rest or exertional angina with more than two attacks in 1 month following a 6-month asymptomatic period.
- 2) **Worsening angina:** Pre-existing angina in which the frequency of attacks triples, the sublingual nitrate dosage must be doubled, or the duration of attack is more than 15 min longer than the previous attack.
- 3) **Changing pattern:** The pattern of anginal attacks undergoes a change — for example, exertional attacks are replaced by attacks at rest or a mixture of both (see below).

Exertional angina: Precipitated by physical activity and/or extreme mental stress.

Rest angina: No apparent precipitating activity and/or occurrence of attacks during sleep. Attacks occur during routine, non-exertional morning activity and are not provoked in the afternoon by the same activity.

Sudden death: Patient was not ill up to 24h prior to witnessed death. Death caused by trauma or damage to other organs was excluded.

Heart failure: Documentation of one or more: pulmonary or systemic edema, congestive liver, or exertional dyspnea in the absence of pulmonary disease.

TABLE II ENROLLMENT OF PATIENTS BY INSTITUTION

<i>Institution</i>	<i>No. of patients</i>	<i>Age</i>	<i>Male/female</i>	<i>Date of CAG</i>
<i>Tokyo University</i>	48	52 ± 9	44/4	Nov. 1978 – Jan. 1983
<i>Hokkaido University</i>	70	49 ± 10	65/5	June 1979 – Aug. 1982
<i>Osaka University</i>	48	55 ± 9	46/2	Nov. 1974 – June 1983
<i>Tohoku University</i>	60	50 ± 12	51/9	Apr. 1973 – Nov. 1982
<i>Kyushu University</i>	76	55 ± 12	67/9	Apr. 1979 – Jan. 1982
<i>Kawasaki Medical College</i>	40	52 ± 9	37/3	Dec. 1977 – Aug. 1982
<i>Jichi Medical College</i>	40	52 ± 8	33/7	Dec. 1976 – May 1980
<i>Fujita Gakuen University</i>	56	54 ± 9	48/8	Aug. 1979 – Mar. 1983
<i>Tokyo Women's Medical College</i>	51	54 ± 8	42/9	Mar. 1980 – Feb. 1982
<i>Total</i>	522	52 ± 10	466/56	Apr. 1973 – Mar. 1983

mented coronary artery disease.

PATIENTS AND METHODS

The protocol was designed in March 1979, with the cooperation of 9 institutions that together, cover a wide area of Japan (Fig. 1). The patients enrolled were less than 70 years of age, and had all undergone satisfactory coronary arteriography (CAG). The diagnosis of ischemic heart disease was made on the basis of clinical, electrocardiographic, coronary arteriographic, and left ventriculographic findings. All patients had experienced at least one attack of myocardial infarction (MI) or angina pectoris as defined in Table I.

Evaluation of coronary arteriography and left ventriculography

Right and left coronary arteries were viewed from multiple directions by means of either Judkins' or Sones' technique. Left ventriculography (LVG) was projected at a 30 degree right anterior oblique angle for evaluation of abnormal wall motion and calculation of the left ventricular ejection fraction. Coronary arterial stenosis and abnormal wall motion were assessed by more than three experts at each institution, according to guidelines from the American Heart Association Committee report.⁹ The criteria for significant stenosis were, 1) 76% or greater reduction of the luminal diameter of the major proximal coronary arteries, and 2) 51% or greater reduction of the left main trunks.

The left ventricular ejection fraction (EF) was calculated by Simpson's method. However, the

absence of an appropriately evaluated ejection fraction, due to the occurrence of arrhythmia during LVG or inadequate concentration of contrast medium, did not mandate exclusion from the study, provided that the coronary arteries were properly assessed and met the criteria. In such cases, the LVG findings were termed "inappropriate".

The patients' demographic data, clinical findings, medical history, results of blood testing, electrocardiography, chest X-ray, and cardiac catheterization were recorded on special forms at the time of enrollment. Follow-up data, including patient survival or death, non-fatal MI, surgical procedures, episodes of unstable angina, arrhythmia, heart failure, medication, and appropriateness on visiting physicians, were updated every 6 months and all information was stored in a computer (Hitac M220H, Hitachi, Tokyo) at Jichi Medical School. The definition of various cardiac events is given in Table I.

Analysis of data

Chi-square tests, including Fisher's exact test and Wilcoxon's T test, were used for comparison of categorized variables, and one-way analysis of variance for numerical variables such as age. Multiple regression analysis was used for multivariate. For the life table analysis, the Kaplan-Meiers test was employed. A p value of less than 0.05 was considered significant.

RESULTS

By June 1983, 466 male and 56 female patients were enrolled. The first 70 patients

TABLE III DEMOGRAPHIC AND CLINICAL DATA OF 491 MEDICALLY TREATED PATIENTS

	No. (%) of patients	Data unavailable ^{A)}
<i>Age (years)</i>		
— 39	43 (9)	
40 — 49	123 (25)	
50 — 59	207 (42)	
60 — 70	118 (24)	
<i>Sex</i>		
Male	437 (89)	
Female	54 (11)	
<i>Occupation</i>		40
Salaried (white collar)	175 (35)	
(blue collar)	95 (19)	
Farmer	23 (4)	
Housewife	25 (5)	
Merchant	9 (2)	
Retired and freelance	55 (11)	
Other	69 (14)	
<i>Angina alone</i>	212 (43)	
<i>MI</i>	279 (57)	
Recent MI	228 (46)	
Old MI	51 (10)	
Transmural MI	254 (52)	
Subendocardial MI	25 (5)	
Anterior MI alone	141 (29)	
Inferior MI alone	111 (23)	
Anterior + Inferior MI	27 (5)	
<i>Number of diseased coronary arteries ($\geq 76\%$)</i>		
No significant stenosis	187 (38)	
Stenosis $\leq 50\%$	117 (24)	
51 — 75%	70 (14)	
One-vessel disease	216 (44)	
RCA	63 (13)	
LAD	134 (27)	
LCX	19 (4)	
Two-vessel disease	60 (12)	
RCA & LAD	29 (6)	
LAD & LCX	19 (4)	
LCX & RCA	12 (3)	
Three-vessel disease	14 (3)	
Left main trunk disease	14 (3)	
<i>Ejection fraction</i>		
$\leq 34\%$	21 (4)	
35 — 49%	81 (17)	
50 —	292 (59)	
Inappropriate	97 (20)	
<i>Left ventricular end-diastolic pressure (mmHg)</i>		28
≤ 11	225 (46)	
12 — 18	173 (35)	
19 —	65 (13)	
<i>Cardiac index (l/min/M²)</i>		126
≤ 2.2	15 (3)	
2.3 —	350 (71)	

(continue)

	No. (%) of patients	Data unavailable ^{A)}
Cardiothoracic ratio		50
≤ 50%	286 (58)	
51 – 55%	98 (20)	
56 –	57 (12)	
Arrhythmias (+)	104 (21)	8
Premature ventricular contraction		8
Infrequent	63 (13)	
Multiple	8 (2)	
Ventricular tachycardia	8 (2)	
Supraventricular tachycardia and atrial fibrillation	14 (3)	
Sinus bradycardia	8 (2)	
Atrioventricular block		5
First degree	31 (6)	
Severer	0 (–)	
Right bundle branch block	4 (1)	7
Left anterior hemiblock	6 (1)	7
Associated condition/coronary risk factors		
Cerebrovascular disease	32 (7)	4
Aortic disease	7 (1)	7
Renal disease	20 (4)	4
Lung disease	9 (1)	6
Perivascular disease	11 (2)	5
Valvular disease;		
Mitral regurgitation	11 (2)	
Mitral stenosis	2 (1)	
Aortic regurgitation	2 (1)	
Family history of heart disease	71 (14)	20
History of heart failure	32 (7)	20
Diabetes mellitus	97 (20)	20
Syphilis	11 (2)	15
Hypertension	192 (39)	6
Hyperuricemia (> 7.0 mg/100 ml)	133 (27)	18
Hypercholesterolemia (> 230 mg/100 ml)	110 (22)	10
Hypertriglyceremia (> 160 mg/100 ml)	164 (33)	21
Smoking (≥ 1 package/day)	284 (58)	80

LAD = left anterior descending artery; LCX = left circumflex artery; MI = myocardial infarction; RCA = right coronary artery. A) Data unavailable = number of patients with description as to each item.

were retrospectively enrolled during April of 1979, when the study was begun, and thereafter enrollment was prospective. Details of enrollment at each institution are provided in Table II. The average age was 52 ± 10 years, 31 patients underwent CABG or left ventricular aneurysmectomy within 3 months of CAG and 491 patients were medically treated for the duration of the follow-up period. In the 31 CABG patients, CABG rendered coronary arteries or anginal attacks refractory to medication, and those who underwent left ventricular aneurysmectomy had severe heart failure and life-threatening ar-

rhythmia. The background data of the 491 medically treated patients are listed in Table III. Those under 40 years of age constituted 9% of the 491 patients. The youngest was a 18 year old patient with Kawasaki disease, who was the only one with this disease enrolled. The population was predominantly (89%) male, and 54% were salaried employees. In the 57% who experienced MI, most occurred within 3 months before CAG. The 43% who did not have MI did experience angina pectoris. Of the 187 patients who did not have significant coronary arterial stenosis, 70 had 51–75% stenosis of the proximal coro-

Fig.2. Cardiac events 522 enrolled patients. MI = myocardial infarction; unwitnessed death = patient had not been examined for more than 3 months prior to death.

TABLE IV CUMULATIVE INCIDENCE OF CARDIAC MORTALITY AND MORBIDITY

	Year				
	First	Second	Third	Fourth	Fifth
Cardiac death	1.6%	2.4%	3.9%	5.5%	5.7%
Nonfatal MI	1.0%	1.4%	2.9%	3.3%	3.7%
Cardiac event	2.6%	4.1%	6.7%	8.1%	9.4%

Cardiac event = cardiac death or nonfatal MI

nary arteries. Thirty-seven patients had coronary spasms without organic stenosis, and 30 had obvious MI not attributable to organic coronary lesions. The left ventricular EF could not be precisely evaluated in 97 patients. Ninety percent of the patients had one or more coronary risk factors, and 13% had other diseased organs. The background data did not differ significantly among the 9 institutions.

During the average follow-up period of 48.7 ± 19.6 months, 40 of the 491 medically treated patients died. Six were non-cardiac related deaths, (cancer, 4; suicide, 1; and traffic accident, 1). Three patients died after more than 3 months without observation, and no details other than the dates of death are known. There were 31 cardiac deaths and 20 non-fatal MI. Since 3 patients died more than 2 months

after the non-fatal MI attack, a total of 48 patients (9.8%) out of 491 medically treated patients was considered to have experienced cardiac events (Fig. 2). The cumulative mortality and morbidity rates are listed in Table IV. The occurrence of cardiac events was highest in the first year. The causes of cardiac death were documented MI in 13 patients, heart failure in 4, and sudden death in 14. Forty-seven patients (9.6%) had heart failure, and 40 (8.1%) had an arrhythmia severe enough to warrant hospitalization. Of the 173 patients (35.2%) who experienced episodes of unstable angina, 10 underwent CABG late in the follow-up period because their angina was refractory to medical treatment. Complications involving other organs, such as cerebrovascular disease, occurred in 12 patients (2.5%).

TABLE V UNIVARIATE ANALYSIS

Categories	No.	Cardiac death	Cardiac event	Cardiac event/ unstable angina
<i>Disease of other organs (Chi-square test)</i>				
Cerebrovascular (0)	455	23 (5%)	41 (9%)	177 (40%)
(+)	32	7 (22%)*	7 (22%)+	19 (59%)*
Renal (0)	467	25 (5%)	39 (8%)	183 (39%)
(+)	20	5 (25%)+	9 (45%)+	13 (65%)*
<i>Coronary risk factors/associated conditions (Chi-square test)</i>				
Hyperuricemia (0)	340	12 (4%)	24 (7%)	141 (41%)
(+)	133	15 (11%)*	20 (15%)+	50 (38%)
<i>No. of risk factors</i>				
0 – 2	300	16 (5%)	22 (7%)	118 (39%)
3 –	180	15 (8%)	26 (14%)*	80 (44%)
<i>History of heart failure</i>				
(0)	429	19 (4%)	36 (8%)	171 (40%)
(+)	42	10 (24%)+	10 (24%)+	9 (21%)*
<i>Numbers of diseased coronary arteries (Wilcoxon test)</i>				
0VD	187	6 (3%)	11 (6%)	70 (37%)
1VD	216	9 (4%)	19 (6%)	82 (38%)
2VD	60	8 (13%)	10 (17%)	27 (45%)
3VD + LMT	28	8 (29%)+	8 (29%)+	19 (68%)*
<i>Left ventricular ejection fraction (Wilcoxon test)</i>				
– 34%	21	4 (19%)	5 (24%)	8 (38%)
35 – 49	81	3 (4%)	4 (5%)	32 (40%)
50 –	292	19 (7%)	28 (10%)*	114 (39%)
<i>Cardiothoracic ratio (Wilcoxon test)</i>				
– 50%	286	11 (4%)	20 (7%)	113 (40%)
51 – 55	98	9 (9%)	14 (14%)	45 (46%)
56 –	57	9 (16%)+	12 (21%)+	26 (46%)*

0VD = no significant stenosis; 1VD = one-vessel disease; 2VD = two-vessel disease; 3VD = three-vessel disease; LMT = left main trunk disease. * $p < 0.05$; ** $p < 0.02$; + $p < 0.01$; ++ $p < 0.001$

Of the 31 surgically treated patients, four died and one had a non-fatal MI attack within 3 months of surgery. The drop-out rate within the first year was 4.3%.

The significant predictive factors for major cardiac events (cardiac death and non-fatal MI) were: the number of diseased coronary arteries, the presence of other diseased organs, such as renal or cerebral disease; the cardiothoracic ratio; a history of heart failure; and the left ventricular ejection fraction (Table V). Among the coronary risk factors, only hyperuricemia and the total number of risk factors in a given patient were significant predictors of major cardiac events. In terms of all ischemic events (cardiac death, non-fatal MI, and unstable angina), coronary risk factors were not significantly predictive; the

patients without a history of congestive heart failure (CHF) had more ischemic events than those with such a history.

Multivariate analysis was applied to the nine variables listed in Table V using the information from 354 patients whose data was complete. Neither the background factor nor the mortality (6.7%) and/or morbidity rates (9.9%) of these patients differed significantly from those of the total population of 491 patients. The significant predictors of cardiac death and major cardiac events were the number of diseased coronary arteries, the presence of renal and/or cerebral disease, and the cardiothoracic ratio (Table VI). There was correlation, though not significant, between the history of heart failure, cardiothoracic ratio, and EF ($r > 0.36$).

TABLE VI MULTIVARIATE ANALYSIS OF MORTALITY AND MORBIDITY

Categories	T-values	
	Cardiac death	Cardiac event
No. of diseased coronary arteries	(1) 4.7070 ⁺⁺	(1) 3.7446 ⁺⁺
Presence of other organ disease	(2) 3.0111 ⁺	(3) 2.0328 [*]
Cardiothoracic ratio	(3) 2.5348 ^{**}	(2) 2.4812 ^{**}
Sex	(4) 1.8393	(4) 1.5901
History of heart failure	(5) 1.6024	(8) 0.5388
Hyperuricemia	(6) 1.0896	(9) 0.3942
Age	(7) 1.0107	(5) 1.0334
Presence of myocardial infarction	(8) 0.5624	(7) 0.5799
Ejection fraction	(9) 0.5422	(6) 0.7125
Multiple correlation coefficient	0.4178	0.3372

Numbers in parentheses indicate the order.

* $p < 0.05$, ** $p < 0.02$, + $p < 0.01$, ++ $p < 0.001$

The survival curves according to the number of significantly diseased coronary arteries are shown in Fig. 3. The 5-year survival rate was 95% for patients without significant coronary artery disease and those with single-vessel disease, 84% for those with two-vessel disease, 62% for those with three-vessel disease, and 78% for those with left main trunk disease. There were no

Fig. 3. Survival curves according to the number of diseased coronary arteries. OVD = no significant stenosis; 1VD, 2VD, and 3VD = one-, two-, and three-vessel disease; LMT = left main trunk disease. Differences in length of survival were significant between OVD and 2VD, 3VD, and LMT, between 1VD and 2VD, 3VD, and LMT, and between 2VD and 3VD ($p < 0.05$).

significant differences between the rate of cardiac death and the major cardiac event according to the specific coronary artery involved (right coronary artery, RCA; left anterior descending artery, LAD; and left circumflex artery, LCX) in patients with one-vessel disease. The cumulative rate of cardiac events was 6.3% in RCA, 7.5% in LAD, and 15.8% in LCX. In specific combinations of diseased coronary arteries, none were significant in this respect in patients with two-vessel disease (RCA and LAD, 21%, LAD and LCX, 21%; and LCX and RCA, 0%). The severity of stenosis in patients with 51–75% stenosis in the major proximal coronary arteries, but not significant stenosis, and in patients with one-vessel disease did not show any significant difference ($\leq 50\%$; 2%; 51% $\leq$ and $\leq 75\%$; 10.0%, 76% $\leq$ and $\leq 90\%$; 5.3%, 91% $\leq$; 9.5%). When the criterion of 51% or more was applied for significant stenosis, the 5-year survival rates were 98% for patients without significant stenosis and 94%, 88%, and 84% for those with one-, two-, and three-vessel disease, respectively. The survival rates of patients with one- and two-vessel disease ($\geq 76\%$) who had 51–75% stenosis in another major coronary artery were not higher than those without stenosis in another artery. The 5-year survival rate of patients with three-vessel and/or left main trunk disease who had an EF of less than 50% was 64.3% which was significantly lower than that of patients with a higher EF (74.8%) ($p < 0.05$).

The 3- and 5-year survival rates of the 70 patients retrospectively entered into the study,

were 88.9% and 83.9%, respectively, and in the remaining 421 patients, 97.2%, and 94.4%, respectively. When the number of diseased coronary arteries was compared, the difference was significant only in patients with three-vessel disease. That is, all four deaths among retrospectively-enrolled patients occurred within 36 months, whereas the 5-year survival rate of the 10 patients who had CAG after that time was 90.0% ($p < 0.001$). The four retrospectively-enrolled patients had greater cardiothoracic ratios ($\geq 50\%$) and lower EF ($< 50\%$) than the 10 prospectively-enrolled patients, however these differences were not significant. The 5-year survival rates for patients with significant coronary stenosis, those with one- and two-vessel disease, and those with left main trunk disease were 95.8%, 92.3%, 70.0%, and 75.0%, respectively for the patients entered retrospectively, and 96.6%, 96.3%, 86.1%, and 78.8% for those studied prospectively. The differences were not significant.

DISCUSSION

This was the first multi-center study conducted in Japan on the natural course of patients with ischemic heart disease in whom coronary artery disease was thoroughly assessed. In studies done in Japan before 1971, the 5-year cardiac mortality rate was reported to be between 19 and 25%⁶⁻⁸. The number of enrolled patients was 400–700, and the findings on the status of coronary arteries were not included. In a study of 563 patients conducted between 1977 and 1983 at a single institution, Saito et al⁵ observed a 12% 5-year cardiac mortality rate. They examined CAG in only about one half of the patients however, and the number of diseased coronary arteries did not significantly correlate with cardiac death or the major cardiac events. The overall cardiac mortality rate of the present study at 5 years (5.7%) is lower than that previously reported in Japan. However, in the 70 retrospectively-enrolled patients, who underwent CAG before April 1979, the rate was 15.8% which is slightly higher than that reported by Saito et al and lower than that of earlier reports. It is possible that differences in the study populations account for the variability in results.

The survival rates according to the number of diseased coronary arteries in the present study were similar to those of 20,088 medically treated patients in a coronary artery surgery study

(CASS) conducted from 1975–1979, reported in 1982,¹⁰ in which 70% or greater stenosis was regarded as significant coronary disease. In that study the 4-year survival rates were 97% for patients without significant coronary stenosis and 92%, 84%, and 68% for those with one-, two-, and three-vessel disease, respectively, whereas the rates of this study were 97%, 94%, 86%, and 64%, respectively. The 421 patients in this study who underwent CAG between 1979 and 1983 had 4-year survival rates of 97%, 96%, 92%, and 90%, respectively, which might reflect lower cardiac mortality in patients with multi-vessel disease, although in our study the proportion of patients with multi-vessel disease (17.9%) was smaller than that in the CASS (50%). The results of the CASS were much more favorable than those of earlier U.S. studies (1973–1976),^{11,12} and ours in Japan. Future studies in Japan should include appropriate significant coronary artery disease, and the impact of multi-vessel disease should be studied in greater depth.

The importance of length and location of coronary stenosis, as described by Humphries et al,¹³ was not addressed in this study. However, we found that the severity of coronary artery disease alone was not a significant predictor of cardiac events in patients with one-vessel disease. The presence of other diseased organs in particular renal and/or cerebral artery disease, and a cardiothoracic ratio of greater than 50% appeared to be important as predictors of cardiac events. The lower EF was the significant predictor for the evolution of major cardiac events only in patients with three-vessel and/or left main trunk disease, as was the case in the CASS. Factors associated with the progression of arteriosclerosis, such as hyperlipidemia and hypertension,¹⁴⁻¹⁶ did not correlate with the occurrence of cardiac death or non-fatal MI. For this reason, it is possible that these associated disorders might have been well controlled. And therefore, the initial abnormal conditions might not have been good predictors. However, these and other risk factors, such as diabetes mellitus and smoking, should be studied further in terms of their severity and the effects on control in protocols in which the above-mentioned major three predictors are matched.

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REFERENCES

1. KEY A: Seven countries — a multivariate analysis of death and coronary heart disease. Harvard University Press, Cambridge, 1980, p 34
2. OMAE T, UEDA K, KIKUMURA T, SHIKATA T, FUJII I, YANAI T, HASUO Y: Cardiovascular deaths among hypertensive subjects of middle to old age: a long-term follow-up study in a Japanese community. In *Hypertension in the Young and the Old*, ed by ONESTI G, KIM KE, Grunne & Stratton, New York, 1981, p 285
3. GORE I, NAKASHIMA T, IMAI T, WHITE PD: Coronary atherosclerosis and myocardial infarction in Kyushu, Japan and Boston, Massachusetts. *Am J Cardiol* 10: 400, 1962
4. UEMURA K, PISA Z: Recent trends in cardiovascular disease mortality in 27 individualized countries. *World Health Stat Q* 38: 142, 1985
5. SAITO M, FUKAMI K, HIRAMORI K, HAZE K, SUMIYOSHI T, KASAGI H, HORIBE H: Long-term prognosis of patients with myocardial infarction: Is mortality and morbidity as low as the incidence of ischemic heart disease in Japan? *Am Heart J* 113: 891, 1987
6. KATO K, TAKAHASHI N, WATANABE E, OHTA A, SUZUKI K, UCHIDA E, ARAYA F, WATANABE T, HAKU R, IINUMA H, FUJII J, KOYAMA S: Clinical courses and prognosis in patients with angina pectoris. *Shinzo* 4: 865, 1972 (In Japanese)
7. TAKAHASHI N, OHTA A, WATANABE E, UCHIDA E, ARAYA F, WATANABE T, HAKU R, IINUMA H, FUJII J, SUZUKI K, KOYAMA S, KATO K: Clinical course and long-term prognosis of Myocardial infarction. *Shinzo* 6: 499, 1974 (In Japanese)
8. Report of the Committee on the Criteria of the Heart Disease and Electrocardiogram: Prognostic value of various electrocardiographic features. *Jpn Heart J* 4: 239, 1963
9. AUSTEN WG, EDWARDS JE, ERYE RL, GENSINI GG, GOTT VL, GRIFFITH LSC, McGOON DC, MURPHY ML, ROE BB: AHA Committee report. A reporting system on patients evaluated for coronary artery disease. *Circulation* 51: 1, 1975 (News from AHA).
10. MOCK MB, RINGGVIST I, FISHER LD, DAVIS KB, CHAITMAN BR, KOUCHOUKOS NT, KAISER GC, ALDERMAN E, RYAN TJ, RUSSEL RO Jr, MULLIN S, FRAY D, KILLIP T III: Survival of medically treated patients in the coronary artery surgery study (CASS) registry. *Circulation* 66: 562, 1982
11. BRUSCHEKE AVG, PROUDFIT W, SONES FW: Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. I. Arteriographic correlations. *Circulation* 47: 1147, 1973
12. BURGGRAF GW, PARKER JO: Prognosis in coronary artery disease — angiographic, hemodynamic and clinical factors. *Circulation* 51: 146, 1975
13. HUMPHRIES JO, KULLER FL, ROSS RS, FRIESINGER GC, PAGE EE: Natural history of ischemic heart disease in relation to arteriographic findings. A 12-year study of 224 patients. *Circulation* 49: 489, 1974
14. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 309: 331, 1983
15. MOISE A, THEROUX P, TAEYMAUS Y, WATERS DD: Factors associated with progression of coronary artery disease in patients with normal or minimally narrowed coronary arteries. *Am J Cardiol* 56: 30, 1985
16. KANNEL WB: Hypertension and other risk factors in coronary heart disease. *Am Heart J* 114: 918, 1987